Remarks

Claim Amendments

Applicants have amended claims to expedite prosecution. Specifically, claims 1 and 24 have been amended to a process and system, respectively, that uses a conditioned uncharged untrafiltration membrane (see, e.g., page 11, lines 13-15 of the specification) with uniform pore size between 0.1-100 kDa (see, e.g., page 4, last full paragraph of the specification). Claim 2 and new claim 26 have been directed to a process and system, respectively, wherein the molecular weight cut-off is 20 kDa (see, e.g., Example 1, page 15, 3rd line from the bottom). Claim 7 and new claim 27 have been directed to a process and system, respectively, wherein the molecular weight cut-off is 1 kDa (see, e.g., Table 3 on page 30). The dependent claims have been amended accordingly to refer to the conditioned ultrafiltration membrane. Additionally, claim 1 has been amended to comprise steps (a) and (b) to perfect antecedent basis for claims referring to step (a). New claims 28 and 29 are directed to embodiments with specific membrane conditioning requirements with salt solution (claim 28) and with salt solution comprising potassium or sodium chloride (claim 29) (see, e.g., page 11, second full paragraph). Claim 21 has been amended to perfect antecedent basis for the term "compartment" (see, e.g., page 6, 5th paragraph from the top). In claim 18, the superfluous "where" has been deleted. The remaining amendments are typographical or grammatical. Claim 8 has been cancelled without prejudice.

Accordingly, Applicants respectfully submit that no new matter has been introduced by the amendments or the new claims and their entry is respectfully requested.

Claim Rejections - 35 USC § 112, first paragraph, written description

Claims 1, 2, and 4-25 were rejected as allegedly not complying with 35 U.S.C. §112, first paragraph, written description requirement. Specifically, the examiner contended that the specification does not provide written description support for the membrane pore sizes "greater than 100 Daltons" and "greater than 500 Daltons."

Applicants respectfully disagree because the specification gives a particular range of 0.1-100 kDa, 0.1-100 Daltons, and specific examples with 1000 Daltons and 20 kDa. Moreover, the specification describes that different cut-off values can be chosen based on the molecular weight of components one wishes to separate. However, to expedite prosecution, applicants have amended claims 1, 2, 4-25 as described, *supra*. The claims as amended refer to molecular weight cut-off ranges and values that have been explicitly disclosed in the specification.

In view of the amendments, Applicants respectfully submit that the rejection has been rendered moot.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4-10, 13-17, 20, and 22-23 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jain (US 4,322,275) in view of Tye (US 3,046,211) and further in view of Akashe and Laustsen (US 5,437,774). Specifically, the examiner contended that Jain teaches the process in general, although without teaching that no pressure is used but that Tye describes an electrodialysis cell operated with no pressure differential between the cell compartments. (col. 3, lines 33-45).

Applicants respectfully submit that the rejection should be withdrawn for the following reasons.

Applicants have amended the claims to embodiments wherein one of the membranes in the electrodialysis cells is a **conditioned uncharged ultrafiltration** membrane. As discussed in the specification on page 3, first full paragraph, while Ahlgren (U.S. Patent No. 4,123,342 also cited in the specification) report an ultrafiltration and electrodialysis method and apparatus, their system has a severe drawback. Specifically, inclusion of the ultrafiltration process significantly increases the resistance of the system, and requires large amount of energy. However, Applicants have surprisingly found that if an ultrafiltration membrane in an electrodialysis cell is **conditioned**, resistance can be significantly reduced, thus making a combined electrodialysis/ultrafiltration cell usable and applicable for large scale processes which was not thought to be possible before (page 11, second full paragraph of the specification). The cited prior art does not teach the element of using a conditioned UF membrane in the system or process.

Applicants further submit that a skilled artisan would also not have been motivated to combine the references to arrive at the method as presently claimed.

To support the statement, Applicants submit a 2nd Declaration under 37 C.F.R. 1.132 by Dr. Bazinet ("2nd BD") describing the problem of resistance and the scientific facts why a skilled artisan would not have combined the cited references to arrive in the currently claimed method. Moreover, Applicants submit a Declaration under 37 C.F.R. 1.132 by professor Gérald Pourcelly ("PD") corroborating the description of Laustsen in the BD and describing how Laustsen particularly teaches against using electrical current alone when a system comprises both ED and UF membranes. Both Dr. Bazinet and professor Pourcelly are experts in the field of membrane separation techniques, professor Pourcelly particularly works at the European Membrane Institute in Montpellier (IEMM).

As explained by Dr. Bazinet, membrane separation processes are based upon selective permeability of one or more of the liquid constituents through a **membrane** according to a **driving force**. (Par. 9 of the 2nd BD.)

The **membranes** can be (1) porous, such as filtration, e.g., ultrafiltration membranes, and (2) non-porous, such as electrodialysis membranes. (Par. 10 of the 2nd BD.)

The **driving forces** that allow separation of molecules through the membranes include (1) pressure difference which is used to drive molecules through a porous or filtration membranes, such as in ultrafiltration membrane, and (2) electrical potential which is used in connection of non-porous ion-exchange membranes to separate molecules according to their charge. (Par. 11 of the 2nd BD.)

Pressure has been used in driving molecules through porous or filtration membranes because porous or filtration membranes are relatively thick and conduct electricity very poorly. Thus porous membrane would not be expected to pass molecules effectively through with electrical force alone. (Par. 12 of the 2nd BD.)

Moreover, if one were to consider using only electrical current, one would not expect such a system to work. This is because of the **known low conductivity of the UF membrane** would be expected to result in high energy consumption in such system. Increasing the amount of electrical current in such high energy consumption system would eventually be expected to lead to water dissociation. Water dissociation in turn would be expected to result in a drastic pH increase at the CEM-diluate and AEM-concentrate interfaces and a proportional decrease at the AEM-diluate and CEM concentrate interfaces. Such pH changes would be problematic in, e.g., protein purification as proteins are susceptible for denaturation as the pH changes. Moreover, it has also been shown that a higher electric field does not allow separation between different small. (Par. 13 of the 2nd BD.)

Jain, Tye and Akashe only describe systems that have electrodialysis (ED) membranes, and not filtration membranes in their disclosures. Because of the above-explained significant differences in the qualities of ED and filtration, such as UF membranes, these references cannot be applied to a combination system with completely different physical requirements.

As stated by Dr. Bazinet, of all the references cited by the examiner, only Ahlgren and Laustsen appear to describe a system, which combines a use of ED and some sort of a filtration membrane in some way. Both **Ahlgren and Laustsen specifically use pressure** to drive molecules through the filtration membrane. None of the remaining cited art describes a system with filtration membranes, such as UF membranes as currently claimed. (Par. 14 of the 2nd BD, emphasis added).

None of the cited references also provides description to teach or suggest that electrical forces alone would be suitable for the use with a filtration membrane, particularly with a UF membrane as currently claimed. Further, none of the cited references provide any guidance why one would expect electrical current to work in view of the known problems associated with the low electrical conductivity of the filtration membrane, such as UF membrane. (Par. 15 of the 2nd BD.)

As evidenced by, e.g., Ahlgren, cited by the examiner, separation using **UF membranes** has traditionally used **pressure as driving force**. Ahlgren itself describes a combination of ED and a UF apparatus which uses significant amount of pressure. Ahlgren also states that "... cells 33c are suitably supported so that they can withstand the **pressures commonly employed in filtration systems**, e.g., on the order of 10-100 pounds psi or more." (Par. 16 of the 2nd BD.)

In paragraph 17 of the 2nd BD, Dr. Bazinet noted that in the Office Action, the examiner stated that

> ...it would have been obvious to one with ordinary skill, in the art at the time of filing to modify the method of Jain by operating the cell with **no pressure differential** between the cell compartments as taught by Tye, **because this would optimize the flow rate through the membranes** from the concentrating liquid to the desalting liquid... .

In paragraph 17 of the 2nd BD, Dr. Bazinet noted that on page 11, the examiner also stated that

> Even if Jain is interpreted as being silent on whether the neutral membrane is a filtration membrane, it would be obvious ... to apply the teachings of Laustsen to the process of Jain, as both Jain and Laustsen are drawn to methods of separating proteins by electrodialysis.

The examiner interpreted that the neutral membrane in Jain is a filtration membrane. However, this statement ignores the scientific facts in that this is not so. The combination of Jain with Tye only teaches a system with ED membranes, not a combination of ED with a filtration, particularly, UF membrane. Neither Jain nor Tye use a system which combines ED and a filtration membrane to separate molecules. (Par. 19 of the 2nd BD.)

In paragraph 20 of the 2nd BD, Dr. Bazinet further stated that, contrary to the examiner's statement, in col. 3 lines 33-36 **Tye does not describe a filtering system without pressure differences**. Tye specifically talks about **uniform pressure differences** explicitly **requiring pressure difference to exist** between the ED membrane bound compartments. Lines 33-46 of Tye (partially cited by the examiner) read as follows:

> It is clear, therefore, that there will be an optimum rate of flow through the membranes from the concentrating liquid to the desalting liquid with any given liquids in any given cell. It is obviously desirable to try to attain this flow rate in all parts of the cell, and this

> means that **the pressure difference** across the membranes **must be fairly uniform** throughout the cell… it is possible by adjustment of flow rates and valves, to arrange that the **same pressure difference** exists between the streams 13 and 11 as between the streams 14 and 12, 17 and 15, and 18 and 16, so that the pressure difference across the membranes 0-4 and 6-10 is the same. However, the pressure difference across the membrane 5 is different… (emphasis added)

According to Dr. Baziner, an expert on this field, this citation does not teach a system without pressure difference, quite the contrary, it **teaches using a uniform or same pressure difference**. (Par. 21 of the 2nd BD.)

According to Dr. Bazinet, even if one were to interpret Tye as describing a system which worked without "pressure differential", in view of the fact that Tye only describes systems which have ED membranes, a skilled artisan knowing that filtration membranes, such as UF membranes have poor conductivity would not have considered using a system without pressure, e.g., a system with electrical current alone in a cell that includes a combination of ED and UF membranes. (Par. 22 of the 2nd BD.)

Dr. Bazinet noted that Laustsen, which appears to describe combined use of a filtration membrane and ED, also specifically **used pressure difference** to drive the molecules through the filtration membrane. (Par. 23 of the 2nd BD.)

As stated by Dr. Bazinet, neither Laustsen, nor Ahlgren, which are the only references that have a UF membrane in the system, describe any conditions that would allow pushing molecules through a UF membrane without pressure differential. (Par. 24 of the 2nd BD.)

According to Dr. Bazinet, in view of the knowledge in the field regarding poor electrical conductivity of filtration membranes, even if one would have considered using no pressure in an ED/UF system, one would not have expected the UF membrane to pass through useful amounts of molecules if no pressure was applied to assist driving the molecules through it. Moreover, one would have expected a high likelihood of denaturation of any proteins one would have tried to isolate with such a method either due to pH or temperature changes as described above. (Par. 25 of the 2nd BD.)

Applicants discovered a way to overcome these problems by conditioning the UF membrane. None of the prior art references teaches a cell that uses ED and a conditioned UF membrane. (Par. 26 of the 2nd BD.)

Thus, the Applicants discovered a particular optimization step that allows the combination of electrodialysis with ultrafiltration to operate without pressure using conditioning of the UF membrane. We discovered that conditioning allowed the molecules to pass through the UF with electrical current

only, without running into the requirement of high energy consumption and problems associated with it. (Par. 27 of the 2nd BD.)

Professor Pourcelly particularly commented on the teachings of Laustsen as Laustsen appears to describe some systems that combine ED and UF membranes. However, professor Pourcelly concluded that it is his expert opinion that Laustsen cannot be viewed as describing a filtration system that works without application of pressure when the system has a combination of ED a filtration membrane, such as a UF membrane, and further, why a scientist in the area of membrane sciences would not have expected a system as described in Laustsen, or any other system that had a combination of ED and filtering membranes, to work if no pressure would be applied. (Par. 6 of PD).

According to professor Pourcelli, It is well known that filtration membranes, such as UF membranes have poor conductivity. (Par. 7 of PD).

Professor Pourcelli continued that while Laustsen appears to describe combined use of a filtration membrane and ED, Laustsen specifically used pressure difference to drive the molecules through the filtration membrane whenever his system had a filtration membrane. (Pars. 8-9 of PD).

In paragraph 10 of PD, professor Pourcelli describes that, Laustsen stated that:

> "by **controlling** electrical potential **and differential pressure** across the separation and the retention membrane, one of the molecular species can be selectively passed through the separation membrane into the dialysate while the other of the molecular species is contained between the separation and retention membranes in the aqueous media. (Col. 2, lines 50-56).

Professor Pourcelli also stated that although Lautsen describes that in certain circumstances the use of pressure can be optional (col.2, line 60 and col. 5, lines 57-58), a scientist in the membrane sciences, even to this day, would view this statement as lacking credibility if it were to be considered to relate to systems with both ED and UF filters, especially in view of the conditions used in the Example of columns 11 and 12 of Laustsen. (Par. 11 of PD).

Laustsen teaches a pressure range between 0.1 to 15 psi (col. 8., lines 57-62). In the examples, Laustsen applied pressure 1.6 psi and 0.6 psi with a differential pressure of 1 psi. Laustsen used a voltage of 160V (column 12, line 27) in a cell of 0.5mm spacing between membranes (column 11, line 38) that resulted in an electric field of 533 V/cm. Despite the help of pressure differential in addition to the very high electric field, Laustsen had to use a heat exchanger to maintain temperature below 30°C to avoid denaturation of the proteins. Thus, according to professor Pourcelli, this demonstrates that unlike in the current inventors' method, the process of Laustsen produces significant amount of heat as a result from the current that produces resistance, even with the help of a differential pressue of 1 psi. Production of

heat is a significant problem if one wishes to isolate non-denatured proteins. Thus, nothing in Laustsen or the other references cited by the examiner in the office action describes how to get a protein through a UF membrane without pressure. (Par. 12 of PD).

Professor Pourcelli stated that in his opinion that "there is simply no way" that a person skilled in the art would believe that this process could work under no pressure differential and be suitable for selectively separating molecules with close molecular weights. (Par. 13 of PD), and that it is also his opinion that Laustsen does not describe any conditions that would allow pushing molecules through a UF membrane without pressure differential. (Par. 14 of PD).

Professor Pourcelli concluded that in view of the knowledge in the field regarding poor electrical conductivity of filtration membranes, even if one would have considered using no pressure in an ED/UF system, one would not have expected the UF membrane to pass through useful amounts of molecules if no pressure was applied to assist driving the molecules through it. Moreover, one would have expected a high likelihood of denaturation of any proteins one would have tried to isolate with such a method either due to pH or temperature changes as described above. (Par. 15 of PD).

Both Dr. Bazinet and professor Pourcelli are thus strongly of the opinion that the cited references, alone or in combination, do not teach, suggest or allow one skilled in the art to expect success with a method or a system which combined the use of ED and UF and uses them under conditions that applies no pressure.

In view of the above, Applicants respectfully submit that the rejection of claims 1, 2, 4-10, 13-17, 20, and 22-23 under 35 U.S.C. 103§(a) over Jain in view of Tye, Akashe and Laustsen should be withdrawn.

Claims 11 and 12 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jain, Tye, Akashe, and Laustsen as applied to claim 1 above, and further in view of Canivenc et al (US 6,312,578 B1). The examiner acknowledged that neither Jain ,Tye, Akashe, nor Laustsen explicitly teach that said compounds are physically, chemically or enzymatically hydrolyzed before performing the step of (a) passing at least once a feed solution containing neutral and charged organic compounds through an electrodialysis cell under electrical field, said electrodialysis cell comprising at least one charged membrane, and at least one filtration membrane. However, the examiner cited Canivenc as allegedly teaching hydrolyzing the compounds before performing electrodialysis. The examiner argued that Canivenc teaches that the hydrolysis step improves the depolymerization, yield and converts the oligomers into monomers.

Applicants respectfully submit that the rejection should be withdrawn for the following reasons.

As described, *supra*, the combination of Jain, Tye, Akashe, and Laustsen fails to teach that the ultrafiltration membrane must be conditioned for the system to work without pressure. Moreover, a skilled artisan would not have been motivated to combine the references because the knowledge in the art teaches against using electrical current only as a driving force for UF membranes and one of ordinary skill in the art would not have expected such a combination to work. Canivenc does not cure these deficiencies, as Canivec only describes hydrolyzing the compounds before performing electrodialysis.

Therefore, the combination of the references fails to teach or suggest all the elements of the claims, and moreover does not provide the missing motivation to combine all of the references to arrive to the presently claimed method. Thus the rejection of claims 11 and 12 should be withdrawn.

Claims 18 and 19 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jain, Tye, Akashe, and Laustsen as applied to claim 1 above, and further in view of Yamada et al (US 2006/0065279 Al). The examiner contended that while neither Jain nor Tye nor Akashe nor Laustsen explicitly teach that at least two filtration membranes are used to allow targeted molecular weight separation of said compounds in combination with charge separation, Yamada describes such an arrangement.

Applicants respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

As described, *supra*, the combination of Jain, Tye, Akashe, and Laustsen fails to teach that the ultrafiltration membrane must be conditioned for the system to work effectively without pressure, and prior art teaches against combining these references.

35 U.S.C. 102(b) states in pertinent parts that a person shall be entitled to a patent unless

> (e) the **invention was described in** - (1) an application for patent, published under section 122(b), **by another** filed **in the United States before the invention by the applicant** for patent **or** (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, **except that an international application** filed under the treaty defined in section 351(a) **shall have the effects for the purposes of this subsection of an application filed in the United States** only if the international application designated the United States and **was published under Article 21(2) of such treaty in the English language**;

Yamada was filed in the U.S. on November 5, 2005 as a continuation application of a PCT/JP04/06001 filed on April 26, 2004 **in Japanese** which claims benefit of Japanese applications filed on May 6, 2003 and November 13, 2003. Translation of neither of the Japanese priority applications has

been provided to the U.S. Patent Office. Thus, the earliest priority date Yamada is available as prior art is on the date of the filing of the U.S. application, namely, November 5, 2005. This is after the earliest priority date of the present application, namely, March 1, 2004 which is the filing date of the U.S. provisional application No. 60/548,181.

Accordingly, Yamada should not be applied as prior art against the present application.

As acknowledged by the examiner, the combination of Jain with Tye, Akashe and Laustsen does not explicitly teach that at least two filtration membranes. Even if Yamada were applicable, and one were to construe that Yamada teaches two filtration membranes, which applicants do not consent to, Yamada fails to teach the element that the UF membranes must be conditioned.

In view of the above, the rejection of claims 18 and 19 should be withdrawn.

Claim 21 was rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jain, Tye , Akashe, and Laustsen, and further in view of Liang et al (US 6,649,037 B2). The examiner contended that while neither Jain nor Tye nor Akashe nor Laustsen explicitly teaches that the pH in a compartment is different from pH of other compartments, Liang described that "the pH in an electrodialysis cell compartment may be different from the pH of other compartments" (where the Examiner construed the electrodeionization device and method of Liang et al as equivalent to an electrodialysis device and method)(col. 8, lines 29-41).

Applicants respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

As described, *supra*, the combination of Jain, Tye, Akashe, and Laustsen fails to teach that the ultrafiltration membrane must be conditioned for the system to work without pressure. Liang does not cure this deficiency as it does not teach that the ED chamber comprises a UF membrane, or that the UF membrane must be conditioned. Liang also fails to provide any teaching or motivation for a skilled artisan to use its methods in an ED chamber with UF membrane. Specifically, nothing in Liand counters the prior art teaching that one should use pressure to drive molecules through UF membrane because a UF membrane conducts electrical current poorly.

Therefore, the combination of the references fails to teach or suggest all the elements of claim 21 and the rejection of claim 21 should be withdrawn.

Claim 24 was rejected under 35 U.S.C. 103(a) as being unpatentable over Ahlgren (US 4,123,342) in view of Tye (US 3,046,211) and further in view of Laustsen. The examiner alleged that

although Ahlgren does not explicitly teach that the charged compounds pass under electric forces with no pressure through the filtration membrane, Tye teaches an electrodialysis cell operated with no pressure differential between the cell compartments, and that Laustsen teaches a neutral filtration membrane having a pore size which effects retention of molecules having molecular weights in the range of 200 Daltons to 200 kDa. The examiner also contended that Jangbarwala teaches an electrodialysis cell comprising at least one cationic membrane, at least one filtration membrane, and at least one anionic membrane on the side of the filtration membrane opposed to the side of the cationic membrane.

Applicants respectfully submit that the rejection should be withdrawn for the following reasons.

The combination of Ahlgren and Laustsen as well as Tye has been discussed above. In view of the facts that none of them teach that the UF membrane must be conditioned, a requirement of the amended claims, and in view of the prior art that teaches against using un-pressurized systems in connection with an UF membrane, and allows one skilled in the art not to expect such a method to work, applicants submit that the rejection of claim 24 should be withdrawn. Moreover, Jangbarwala does not overcome the deficiency. Jangbarwala only again describes a system for ED with a particle filtering membrane, not an ED with a UF membrane.

Accordingly, the combination does not disclose all the elements of the claims and moreover, does not allow one skilled in the art to overcome the expectation of failure of a system which uses both ED and UF membrane without pressure.

Therefore, the rejection of claim 25 should be withdrawn.

The examiner alleged that the declaration filed on July 7, 2011 was insufficient to overcome the rejection of claims 1, 2, and 4-23 based upon Jain in view of Tye alleging that

> "it include(s) statements which amount to an affirmation that the claimed subject matter functions as it was intended to function. This is not relevant to the issue of nonobviousness of the claimed subject matter and provides no objective evidence thereof. See MPEP § 716.

The examiner made this assertion without pointing to any specific statements. Applicants respectfully submit that contrary to the examiner's contention, the declaration provides crucial facts to show why a skilled artisan would not have been motivated to combine the references. For example, pars. 6 and 7 provide that Jain does not separate proteins, but rather precipitates them. Moreover these paragraphs provide that contrary to the examiner's interpretation, Jain does not use a filter membrane, as it described salting in and salting out, not filtering molecules through a filter as required by the claims. Par. 14of the Declaration explained that use of a UF membrane in an ED chamber without pressure is

surprising because one would have expected UF not to work without pressure because it conducts current poorly and thus would have been expected not to pass molecules through without pressure.

In view of the above, Applicants respectfully submit that the amended and the new claims are in condition for allowance. Early and favorable action on the merits is requested.

In the event that any additional fees are required with this submission, the Commissioner is authorized to charge Nixon Peabody LLP Deposit Account No. 50-0850.

Date: February 24, 2012

Respectfully submitted,

/Leena H. Karttunen Contarino/

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